UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge
This Document Relates to All Actions	

MYLAN'S MEMORANDUM OF LAW IN OPPOSITION TO PLAINTIFFS' *DAUBERT* MOTION TO EXCLUDE CLASS CERTIFICATION OPINIONS OF ERIC SHEININ, PH.D.

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Pursuant to Federal Rules of Evidence 104, 403, and 702, Defendants Mylan Laboratories Ltd. and Mylan Pharmaceuticals Inc. ("Mylan") submit this memorandum of law in opposition to Plaintiffs' *Daubert* Motion to Exclude Class Certification Opinions of Dr. Sheinin ("Motion").

INTRODUCTION

Dr. Eric Sheinin is a regulatory specialist who has over 50 years of pharmaceutical industry experience—including 30 years working for the United States Food and Drug Administration ("FDA"), and 6 years with the United States Pharmacopeial Convention, Inc. ("USPC"). Mylan retained Dr. Sheinin to offer two narrow opinions pertaining to class certification. ***First***, Dr. Sheinin opines that Mylan's valsartan active pharmaceutical ingredient ("API") manufactured between market entry in 2012 and the recall of Mylan's VCDs in late 2018 complied with all of the applicable standards and specifications that were in place at the time of manufacture, and FDA's subsequent establishment of new standards did not retroactively render Mylan's VCDs adulterated and misbranded. ***Second***, Dr. Sheinin responded to Plaintiffs' expert, Ron Najafi, who opined that Mylan's VCDs were not the generic equivalent of the reference listed drugs, Diovan and Exforge ("RLDs"), due to the presence of NDEA. Dr. Sheinin rebuts this opinion and will testify that the impurity profile of a generic drug has no bearing on whether it is deemed the same as the RLD. Dr. Sheinin also opines that Mylan's VCDs were

approved by FDA to be sold in the U.S. under the Food, Drug, and Cosmetics Act ("FDCA") and related federal regulations at all times prior to the recall.

Plaintiffs' Motion attempts to sidestep Dr. Sheinin's opinions in favor of straw-man arguments and hypotheticals that bely the lack of any credible basis to exclude his testimony. First, Plaintiffs argue that Dr. Sheinin's opinion that Mylan's VCDs met applicable specifications is not relevant or helpful because, according to Plaintiffs, it does not matter whether Mylan's VCDs "technically" met the established specifications prior to 2018 because NDEA was ultimately present. Yet, Plaintiffs ignore Dr. Sheinin's related opinion that revised 2018 specifications for valsartan—following the discovery of the NDEA impurity—did not apply retroactively. Second, Plaintiffs criticize Dr. Sheinin for "failing" to review Mylan's valsartan Drug Master File ("DMF") in its entirety. But, as Plaintiffs acknowledge, Dr. Sheinin did not render a single opinion regarding the adequacy of Mylan's DMF, nor did he opine on Mylan's process for manufacturing VCDs. Indeed, these matters are beyond the scope of the class certification question presently before the Court. As a result, there was no need for Dr. Sheinin to review the full DMF. Third, Plaintiffs argue that Dr. Sheinin's purportedly erroneous "assumption" that NDMA and NDEA are not "genotoxic impurities" formed the foundation of his opinion that Mylan's VCDs met all applicable specifications prior to 2018. To the contrary, Dr. Sheinin made no such assumption in forming his opinions, therefore this argument

is irrelevant. Finally, Plaintiffs attack Dr. Sheinin for concluding that Mylan's VCDs were therapeutically equivalent to the RLD. Notably, Dr. Sheinin offered no opinions regarding therapeutic equivalence in his report. Further, Plaintiffs have yet to prove that Mylan's VCDs were adulterated or not the generic equivalent of the RLD. These issues are heavily contested and do not provide grounds to exclude Dr. Sheinin's testimony.

For the foregoing reasons, Plaintiffs' Motion should be denied in its entirety.

BACKGROUND

Dr. Eric Sheinin is a regulatory professional with a background in organic chemistry. He has spent his 50-year career working at FDA, USPC, and advising pharmaceutical industry clients about the regulatory process. (Sheinin Rep. ¶ 9, Pls.' Mot. Ex. 2 [Dkt. 2036-3]). This includes 30 years working at FDA. (*Id.* at ¶ 11.) During his time at FDA, Dr. Sheinin was the head of the Drug Standards Research Branch, which was responsible for validating the analytical methodology included in new drug applications ("NDAs") and abbreviated new drug applications ("ANDAs"). (*Id.*) Dr. Sheinin was then promoted to lead the Office of New Drug Chemistry at the FDA's Center for Drug Evaluation and Research ("CDER"). (*Id.* at ¶ 14.) In that role, Dr. Sheinin was responsible for overseeing of all the review chemists and review microbiologists in the new drug area. (*Id.*) While at CDER, Dr. Sheinin worked closely with the chemistry, manufacturing, and controls ("CMC")

requirements related to NDAs and ANDAs, as well as working to create guidelines for industry that are still in effect. (*Id.* at ¶ 15.) Likewise, Dr. Sheinin participated in the development of guidelines produced by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH"). (*Id.* at ¶ 17.)

After retiring from FDA, Dr. Sheinin joined USPC as a vice president responsible for overseeing the development of USP standards. (*Id.* at ¶ 18.) Most notably, he was involved in the launch of the USPC program for the verification of the quality of pharmaceutical ingredients used in drug products marketed in the U.S., and worked with regulators worldwide to harmonize monographs related to pharmaceutical products (*Id.*)

Following his 6 years at USPC, Dr. Sheinin entered consulting as president of Sheinin & Associates LLC. (*Id.* at ¶ 18.) All told, Dr. Sheinin has now served as an industry consultant for nearly 15 years, reviewing DMFs, NDAs, ANDAs, and related materials for submission to the FDA, and assisting companies with responses to various types of requests for additional information from regulators. (*Id.*)

Plaintiffs in this MDL assert that due to the presence of NDMA and NDEA impurities in VCDs, those products were adulterated and misbranded. Plaintiffs Rule 23 experts rely upon this assumption to form the basis for their opinions. That includes Dr. Conti's proposed damages model (*see, e.g.*, Pls.' Econ. Loss Br. at 69),

and Dr. Najafi's equivalence theory. It also relates to Defendants' Rule 23 predominance challenges (*see, e.g.*, Pls.' Econ. Loss. Reply Br. at 24 (arguing that state law variations do not defeat class treatment of claims because an adulterated product is "literally non-merchantable in every state")). Dr. Sheinin's discrete opinions also relate to this core issue.

At the outset of his report, Dr. Sheinin offers important background regarding the interplay between the FDCA, the regulations, and USP monographs. Specifically, Section 351 of the FDCA provides that a drug or device shall be deemed to be adulterated if it purports to be or is represented in an official compendium, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium. Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium." Sheinin Rep. at ¶ 39.) Per section 321(j), "[t]he term 'official compendium' means the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them." (*Id.* at ¶ 38.). Accordingly, "if there is a USP monograph for a given drug, an ANDA must meet the requirements set forth in that monograph in order for FDA to approve that application." (*Id.* at 40.)

Against this backdrop, Dr. Sheinin opines that "Mylan's Valsartan USP API continued to meet its specification as well as its DMF specification throughout this

period." (Sheinin Rep. at ¶ 68.) More generally, he also concludes that drug substance or drug product is not considered misbranded or adulterated simply because it contains impurities, ***including*** potentially genotoxic impurities. (*Id.* at ¶ 69.) In order to render these opinions, Dr. Sheinin reviewed the USP Valsartan API monograph that was official until April 30, 2020, which contained no mention of nitrosamine compounds. (*Id.* at ¶ 64.)[1] Accordingly, Dr. Sheinin concludes that "per the USP monograph, there were no tests or acceptance criteria in place with respect to nitrosamine content or testing aimed at detection of nitrosamine impurities." (*Id.* at ¶ 66.) Likewise, Dr. Sheinin reviewed Mylan's DMF impurity specification,[2] and FDA's nitrosamine guidance, and he concludes that there was no requirement for Mylan to control or test specifically for nitrosamine impurities until the origin of FDA's investigation of ARBs in mid-2018." (*Id.* at ¶ 67.) Specifically, FDA's guidance, published years after the first valsartan recall, states "[t]he recent ***unexpected finding*** of nitrosamine impurities, which are probable human carcinogens, in drugs such as angiotensin II receptor blockers (ARBs), ranitidine,

[1] A revised version of the USP Valsartan API monograph became official on May 1, 2020, and likewise contains no mention of nitrosamine compounds or testing. (*Id.* at ¶ 65.)

[2] Although he did not review the DMF in its entirety, Dr. Sheinin testified that he analyzed certificates of analysis related to Mylan's VCDs, which indicated that Mylan was in compliance with all of the acceptance criteria in the DMF. (Sheinin Dep. 173:10-14). Moreover, the mere fact that Mylan's VCDs were on the market from indicates that it met all compendial standards in place at the time, otherwise FDA would not have permitted them to be sold (*Id.* at 279:13-22.)

nizatidine, and metformin, ***has made clear the need for a risk assessment strategy*** for potential nitrosamines in any pharmaceutical product at risk for their presence." (*Id.* at ¶ 70 [emphasis added].) Indeed, in response to the 2018 discovery of NDMA and NDEA in VCDs, CDER developed and implemented a new validated analytical method capable of quantitating NDMA and NDEA at trace levels. (Sheinin Rep. at ¶ 74.) Notably, this new analytical method "is not a routine quality control method typically used to monitor and control impurities in drug substances and drug products." (*Id.* at ¶ 79.) Thus, prior to the development of this method in 2018, the trace levels of NDEA in Mylan's VCDs could not be detected by the testing required as part of Mylan's DMF specification. (*Id.* at ¶ 80.) While Mylan's DMF included a specification for unknown impurities of "not more than" 0.1%, or 1,000 parts per million ("ppm") (*Id.*), the highest level of impurity detected in Mylan's valsartan API—1.57 ppm—was nowhere near this threshold. (*Id.*) Indeed, High-Performance Liquid Chromatography ("HPLC") methods included in the USP monograph would not be capable of detecting impurities at such low levels. (Sheinin Rep. at ¶ 80.) This further supports Dr. Sheinin's opinion that Mylan's valsartan API was within specification at all relevant times. Moreover, **"**FDA's establishment of specifications and standards in mid-to-late 2018 for nitrosamine content does not retroactively render all previously manufactured drug substance or drug product adulterated or misbranded." (*Id.* at ¶ 102.)

Dr. Sheinin also addresses the following opinions proffered by Plaintiffs' Rule 23 expert, Dr. Najafi: (i) "Valsartan containing products that contained NDMA and NDEA were not the generic equivalent of Diovan or Exforge because they contained NDMA and NDEA" (Najafi Rep. ¶ 32); and (ii) "[T]he Valsartan containing products with NDMA and NDEA were not the same as or chemically equivalent to the brand name Diovan or Exforge products because they contained NDMA and NDEA." (*Id.* at ¶ 33). In order to assess Dr. Najafi's conclusions, Dr. Sheinin reviewed the "sameness" requirement enshrined in the FDCA. (Sheinin Rep. ¶¶ 85-88.) He also considered FDA's application of this standard, with which he is intimately familiar based on his 50 years of experience working directly in and around the regulation of pharmaceutical products. Specifically, Dr. Sheinin opined that in approving Mylan's ANDAs for to VCDs, FDA necessarily analyzed Mylan's DMF "and determined that drug product incorporating Mylan Laboratories Ltd.'s Valsartan USP API and manufactured in accordance with the referenced standards and specifications would be considered the same as and bioequivalent to the relevant RLDs for purposes of compliance with the FDCA." (*Id.* at ¶¶ 89-93.) Moreover, "[t]he suppliers of a given API used in an ANDA often utilize a synthetic route that differs from that of the supplier of an API used in the RLD. Because the synthetic process differs it is quite common for a different set of impurities to be present in the API used in an ANDA, *i.e.*, there can be a different impurity profile." (*Id.* at 94.)

Nevertheless, "[t]he fact that a given API contains a different set of impurities does not in itself mean that it differs from the API used in an RLD. This is an evaluation that can only be made by the FDA as the Agency is statutorily tasked enforcing the requirement found in a given USP monograph." (*Id.* at 97.) This directly contradicts Dr. Najafi's core opinion that the presence of NDMA and NDEA—inactive ingredients that have no bearing on sameness or bioequivalence—were not the generic equivalent of Diovan or Exforge. (Sheinin Rep. at ¶¶ 98-101.)

ARGUMENT[3]

Plaintiffs' Motion should be denied because Dr. Sheinin applied a reliable methodology in offering admissible expert testimony that pertains directly to issues that Plaintiffs have made central to their class certification motions.[4] Plaintiffs' scattershot Motion offers no proper basis to exclude Dr. Sheinin's testimony, which is narrow, reliable, and helpful to the trier of fact.

I. Dr. Sheinin's Methodology Was Reliably Applied.

Plaintiffs' primary critique of Dr. Sheinin is that he failed to apply any reliable methodology. (Pls.' Br. at 3.) Specifically, Plaintiffs assert that Dr. Sheinin failed to apply "applicable regulations," and "resorted to making up his own set of facts on

[3] The standards governing the admissibility of expert testimony are set forth in Defendants' Memorandum of Law in Opposition to the Motion to Partially Exclude Opinions of Defense Class Expert Timothy E. Kosty, and are incorporated fully herein.

[4] Plaintiffs concede that Dr. Sheinin is qualified to offer testimony in this case.

which to base his opinions." These arguments are demonstrably false.

With regard to the applicable standard—and unlike Dr. Najafi—Dr. Sheinin references the specific provisions of the FDCA and the regulations that govern the bioequivalence of generic pharmaceutical drugs in his report. (*See, e.g.*, Sheinin Rep. at ¶¶ 85-88: 100-01.) Dr. Sheinin's report also references the FDCA's adoption of USP as the "official compendium," and section 351(b) of the FDCA related to adulteration. (*Id.* at ¶¶ 35-39.) Thus, unlike the invented standards upon which Dr. Najafi bases his opinions, Dr. Sheinin's opinions incorporate the primary standards that are relevant to his inquiry. Further, based on his years of regulatory work, Dr. Sheinin is familiar with and has applied these standards outside of this litigation. In short, Plaintiffs' argument that Dr. Sheinin did not reliably apply the proper standards is meritless.

Plaintiffs also argue that Dr. Sheinin relied on an inaccurate factual record because he failed to review the totality of Mylan's DMF, and failed to accept Plaintiffs' assumptions and hypotheticals regarding disputed issues as fact. First, with regard to the DMF, it was unnecessary for Dr. Sheinin to review this file—which is comprised of thousands of pages of technical data and specifications—in order to offer his narrow Rule 23 opinion regarding whether Mylan's VCDs complied with the compendial requirements for impurities. As Dr. Sheinin readily admits, he offers no opinion on the quality of adequacy of Mylan's DMF (a disputed

factual issue that is not germane to the Rule 23 question). (Sheinin Dep. 53:1-6, Pls.' Mot. Ex. 1 [Dkt. 2036-2].) Rather, his opinion is strictly limited to whether Mylan's valsartan API met the impurity specification as it existed from 2012 to 2018.

Plaintiffs also criticize Dr. Sheinin for failing to accept their assumption that all of Mylan's VCDs were adulterated due to the presence of NDEA. In short, just because Plaintiffs' proffered Rule 23 experts accepted the hypothetical of adulteration as a fact does not mean that Dr. Sheinin was required to do the same. Dr. Sheinin's rejection of Plaintiffs' adulteration hypothetical does not render his opinions irrelevant. And, notably, Dr. Sheinin provides credible opinion testimony as to why Plaintiffs' core assumption of adulteration should be rejected.

Although Plaintiffs accuse Dr. Sheinin of "making up his own set of facts," it is Plaintiffs' that invent an alternate factual record in support of their Motion. For instance, contrary to Plaintiffs' assertion, Mylan never "certified [in its DMF] that its Valsartan API process would create zero (0) NDMA/NDEA." (Pls.' Mot at 6.) Plaintiffs' base this argument on a deliberate misreading of the evidence. Mylan was unaware of the presence, or even the potential, for the formation of NDEA in its VCDs prior to late 2018. As a result, Mylan could not have "certified" that NDEA was not present because its presence was unknown. Just because Plaintiffs repeat this argument *ad nauseum* does not make it true, nor is it relevant to Dr. Sheinin's opinions.

Similarly, Plaintiffs assert that Dr. Sheinin "pretends that NDMA/NDEA are not genotoxic impurities." (Pls.' Br. at 7.) Again, this is irrelevant to Dr. Sheinin's opinions and to the Rule 23 analysis. Plaintiffs also misconstrue the record in support of this argument. Indeed, the specific testimony on which Plaintiffs rely for the false proposition that Dr. Sheinin "pretends" NDEA is not a genotoxic impurity lends no support to Plaintiffs' argument:

> Q. Does the potential presence of NDEA, at levels up to 1.57 parts per million, change your opinion that drug substance manufactured in accordance with the specifications set forth in Mylan's DMF would be compliant with compendial standards?
>
> A. There's not --
>
> MR. DAVIS: Object to form.
>
> Q. Okay. Can you explain why that is?
>
> COURT REPORTER: I'm sorry. I need that answer repeated.
>
> MR. REEFER: Could you repeat your answer, Dr. Sheinin.
>
> THE WITNESS: I think I said, no, it does not.
>
> Q. And can you explain why it does not?
>
> A. Because at 1.57 PPM, it would still meet the acceptance criteria in the test for any other impurity of 0.1 percent.

(Sheinin Dep. 281:2-282:2.)

Plaintiffs' citation to the record is also selective. Dr. Sheinin went on to explain why he relies upon the 0.1 percent impurity specification:

> Q. With respect to your -- the opinion you offered regarding the capabilities of routine testing to detect levels of NDEA as found in some batches of Mylan's drug substance, is it relevant for you to compare the specification set forth in the compendium of not more than 0.1 percent versus the levels of NDEA detected in Mylan's drug?
>
> A. Yes.
>
> Q. How so?
>
> A. The levels that are found in Mylan's API would be well below the .1 percent. So the testing of the impurity -- testing for impurities in the API, it would pass if -- unless – unless there was another impurity of some unknown that was greater than .1 percent.
>
> Q. And --
>
> A. The NDEA or NDMA, if it was present, would be well below .1 percent.
>
> Q. And just, I guess, for purposes of comparing apples to apples, does .1 percent translate to 1,000 parts per million?
>
> A. Yes.

(*Id.* at 286:20-287:20.)

At no point during the foregoing line of questioning—or at any other time during his report or deposition—did Dr. Sheinin suggest or assume anything regarding the genotoxicity of NDEA, which he concedes is beyond his purview. Yet, Plaintiffs base an entire subsection of their brief on this false notion. This is a classic straw-man argument that has no bearing on the admissibility of Dr. Sheinin's opinions. And, in any event, these issues relate to disputed facts and heavily contested interpretations of evidence. Dr. Sheinin's opinions cannot be properly

excluded on this basis.

As Plaintiffs acknowledge, Dr. Sheinin's report provides "a lengthy discussion of DMFs and USP Monographs." (Pls.' Mot at 5.) Plaintiffs attempt to brush over this discussion, but it is not mere window-dressing. Rather, Dr. Sheinin's knowledge of the regulatory process and the relationship between DMF specifications and USP standards, as applied to this case, constitutes his methodology and is reliable. Indeed, Dr. Sheinin's reliance upon his decades of regulatory experience when interpreting and opining on these standards is an accepted methodology where an expert is appropriately qualified. *See, e.g.,* United States v. Li, 819 F. App'x 111, 117–18 (3d Cir. 2020) (citing *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 150–51 (1999)) (expert testimony need not be based on firsthand knowledge or observation where it relies upon knowledge and experience of the expert's discipline); *United States v. Fernandez*, 795 F. App'x 153, 156 n.15 (3d Cir. 2020); *Gold v. State Farm Fire & Cas. Co.*, 880 F. Supp. 2d 587, 596 (E.D. Pa 2012) (same).

Accordingly, Dr. Sheinin applied a reliable methodology based on his review of the relevant standards and evidence, as well as his decades of applicable regulatory experience.

II. Dr. Sheinin's Opinions "Fit" because they Relate Directly to Class Certification Issues.

Plaintiffs Motion also asserts a half-baked argument that Dr. Sheinin's opinions regarding DMF and USP specifications are "completely irrelevant and unhelpful to the jury or Court to resolve any disputed issue." (Pls.' Br. at 4.) In advancing this argument, Plaintiffs completely ignore the purpose of Dr. Sheinin's opinions, which are to address (i) Plaintiffs' erroneous assertion that all of Mylan's VCDs that contained NDEA were adulterated, and (ii) Dr. Najafi's opinion that Mylan's VCDs were not the generic equivalent of the RLDs due to the presence of NDEA. Plaintiffs "fit" argument is predicated entirely upon Plaintiffs' assumption that Mylan's VCDs were in fact adulterated—but, as addressed *supra*, this is a contested issue that has not been resolved. In short, Dr. Sheinin's opinions are plainly relevant to the Rule 23 analysis.

Moreover, Plaintiffs' arguments regarding whether Dr. Sheinin's opinions are relevant and helpful to the trier of fact have little bearing on the admissibility of his opinions for Rule 23 purposes. "The main purpose of *Daubert* exclusion is to protect juries from being swayed by dubious [expert] testimony." *See In re Zurn Pex Plumbing Liab. Litig.*, 644 F.3d 604, 613 (8th Cir. 2011). The trial court's "gatekeeping function" is, therefore, reduced " 'when the gatekeeper is keeping the gate only for himself. *In re Tropicana Orange Juice Mktg. & Sales Pracs. Litig.*, No. CV 2:11-07382, 2017 WL 2362848, at *2 (D.N.J. May 31, 2017) (quoting *United*

States v. Brown, 415 F.3d 1257, 1269 (11th Cir. 2005)); *see also Metavante Corp. v. Emigrant Sav. Bank*, 619 F.3d 748, 760 (7th Cir. 2010) ("usual concerns" of *Daubert* are not present during a bench trial). Indeed, "[a]t class certification, the district court serves as the trier-of-fact and no jury is present. Accordingly, the Court should weigh Plaintiffs' challenge to Dr. Sheinin in light of this consideration, and should deny Plaintiffs' Motion.

CONCLUSION

Dr. Sheinin is qualified, implemented a reliable methodology, and his narrow opinions are relevant to contested Rule 23 issues and ultimately helpful to the trier of fact. Accordingly, the Court should deny Plaintiffs' *Daubert* Motion to Exclude Class Certification Opinions of Dr. Sheinin

Dated: June 2, 2022

Respectfully Submitted:

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CERTIFICATE OF SERVICE

I hereby certify that on June 2, 2022, a copy of the foregoing document was served on all counsel of record via CM/ECF.

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